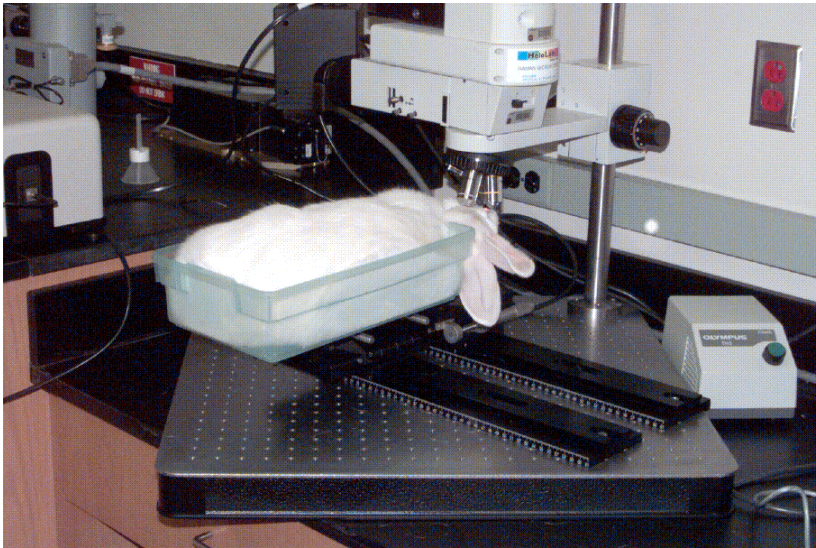


The Pharmacokinetics of the Blood-Brain Barrier: Applications in Chemotherapy and Astronaut Health

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Description

The objectives of this proposal are: (1) to develop a non-invasive instrument for NASA to use in studying the pharmacokinetics of the Blood-Brain Barrier (BBB) in astronauts and (2) to test this technology in an NCI BBB application: adjusting chemotherapy dosages in the treatment of CNS tumors. The pharmacokinetics of the BBB and the blood-aqueous barrier (BAB) has been shown to be highly correlated for many endogenous and exogenous compounds. Our hypothesis is that BAB pharmacokinetics of a non-toxic chemotherapeutic compound, fenretinide, may therefore be used to predict BBB pharmacokinetics both with and without osmotic disruption or these barriers. Resonant-Enhanced Raman Spectroscopy will be used to dynamically measure fenretinide concentrations in the aqueous humor and compared to levels measured simultaneously in the CSF.

Innovative Claims/NASA Significance

- No other non-invasive method for measuring the pharmacokinetics of the blood-brain barrier currently exists.
- Understanding the influence of microgravity on the pharmacokinetics of therapeutic drugs is extremely important to insure and maintain the health of astronauts.
- Fenretinide is a non-toxic but powerful chemopreventative agent that may help protect astronauts from some of the effects of exposure to heavy ion radiation during EVA's or extended missions.

Plans

- Develop non-invasive instrument capable of measuring fenretinide within the AH at concentrations inclusive of those clinically achievable in plasma (1nM - 30 uM).
- Conduct pharmacokinetic studies in rabbits to measure the correlation of fenretinide levels in AH and CSF. Validate instrument performance by comparing with that obtained using invasive techniques.
- If optical exposures necessary to measure fenretinide levels within the therapeutic range is above ANSI standards, conduct optical toxicity studies. Obtain approval for use of the instrument on humans as an investigational device.
- Pharmacologically disrupt the BBB in rabbits and measure changes in the pharmacokinetics of fenretinide in the AH and the CSF. Correlate biochemically determined and non-invasive AH measurements.
- Conduct testing of non-invasive instrument in non-human primates at Baylor College of Medicine under existing protocol. Correlate results with CSF samples obtained from indwelling ports implanted under existing protocol.
- Conduct adjunct clinical trials using Raman instrument to non-invasively measure fenretinide in the AH of cancer patients on open fenretinide protocols. Validate using CSF samples from patients for whom CSF collection is medically indicated (e.g. acute lymphocytic leukemia (ALL)).